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HIV Medicine (2020)

EUROPEAN AIDS CLINICAL SOCIETY (EACS) GUIDELINE (HIV)

2019 update of the European AIDS Clinical Society Guidelines for treatment of people living with HIV version 10.0

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Background

The European AIDS Clinical Society (EACS) Guidelines cover key aspects of HIV management with major updates every two years.

Guideline highlights

The 2019 Guidelines were extended with a new section focusing on drug–drug interactions and other prescribing issues in people living with HIV (PLWH). The recommendations for treatment-naïve PLWH were updated with four preferred regimens favouring unboosted integrase inhibitors. A two-drug regimen with dolutegravir and lamivudine, and a three-drug regimen including doravirine were also added to the recommended initial regimens. Lower thresholds for hypertension were expanded to all PLWH and for cardiovascular disease prevention, the 10-year predicted risk threshold for consideration of antiretroviral therapy (ART) modification was lowered from 20% to 10%. Frailty and obesity were added as new topics. It was specified to use urine albumin to creatinine ratio to screen for glomerular disease and urine protein to creatinine ratio for tubular diseases, and thresholds were streamlined with the Kidney Disease: Improving Global Outcomes (KDIGO) recommendations. Hepatitis C virus (HCV) treatment recommendations were split into preferred and alternative treatment options. The algorithm for management of recently acquired HCV infection was updated and includes recommendations for early chronic infection management. Treatment of resistant tuberculosis (TB) was streamlined with the World Health

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Organization (WHO) recommendations, and new tables on immune reconstitution inflammatory syndrome, on when to start ART in the presence of opportunistic infections and on TB drug dosing were included.

Conclusions

The EACS Guidelines underwent major revisions of all sections in 2019. They are available in four different formats including a new interactive web-based version and are translated into Chinese, French, German, Japanese, Portuguese, Russian and Spanish.

Keywords: antiretroviral treatment, comorbidities, drug–drug interactions, European AIDS Clinical Society (EACS) Guidelines, hepatitis B virus, hepatitis C virus, HIV, opportunistic infections, prescribing in elderly patients

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The European AIDS Clinical Society (EACS) Guidelines

As several countries are lacking or infrequently update national HIV guidelines, the EACS Guidelines have since 2005 provided recommendations that are independent of geographical region and levels of care. Acknowledging that HIV care extends far beyond antiretroviral treatment (ART), the EACS Guidelines also provide guidance on several other key aspects related to HIV management.

In 2019, the EACS Guidelines underwent major revisions of all sections [1]. One of the most essential changes includes a new panel focusing on drug–drug interactions (DDIs) and other prescribing issues in people living with HIV (PLWH) in acknowledgement of the increased ageing of PLWH and increasing risks of polypharmacy.

Bictegravir (BIC) and doravirine (DOR) were released since the last major revision and have been included in all sections. In addition, older drugs that are now rarely used, including several older boosted protease inhibitors (PI/bs), didanosine and stavudine, were removed from most sections.

To ensure easy access to the Guidelines, a new format in the form of an interactive web-based version was introduced (https://eacs.sanfordguide.com) in 2019. The Guidelines remain available in print as a booklet, online as a pdf (https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf) and as a free App for IOS and Android devices produced with the Sanford Group. The EACS Guidelines are translated into Chinese, French, German, Japanese, Portuguese, Russian and Spanish.

The Guideline review process

The Guidelines undergo major revisions every second year, and minor revisions in the years in between, as previously described [2]. Interim updates may be performed in the case of new key data emerging between scheduled updates. Meetings are held at regular intervals but can also be set up at short notice when necessary.

Each of the Guideline sections is created by a panel of experts governed by a three-person leadership group. The Guidelines are managed by a Guidelines Chair and Coordinator; details have previously been described [2]. As also previously reported, the recommendations provided in the EACS Guidelines are based on evidence whenever possible, and, in the rare instances where adequate evidence is unavailable, based on expert opinions [2].

The Guidelines are extensively cross-reviewed by the panellists, and by representatives from the community and from Women Against Viruses in Europe (WAVE). Conflict of interest statements are required for all members and can be provided upon request.

In the following, the most important changes made in version 10.0 for each section of the Guidelines are described.

ART section

In the 2019 version, the layout for initial ART regimens, treatment in pregnancy/women wishing to conceive and in persons coinfected with tuberculosis (TB) were made uniform to ensure consistency.

Before initiating ART, it is recommended to consider if a woman is pregnant or wishes to conceive, and if the person has an opportunistic infection or any potential treatment-limiting comorbidities. In addition, it is recommended to consider if the person is at risk of DDIs or if the person has swallowing difficulties. In all these instances, the Guidelines provide management recommendations.

Among the recommended first-line regimens for ART-naïve PLWH, EACS recommends four preferred options consisting of two nucleoside reverse transcriptase inhibitors [NRTIs; abacavir (ABC)/lamivudine (3TC), tenofovir alafenamide (TAF)/emtricitabine (FTC), tenofovir disoproxil fumarate (TDF)/TFC or TDF/3TC] in combination with an unboosted integrase strand transfer inhibitor [INSTI; dolutegravir (DTG), BIC or raltegravir (RAL)] (Table 1). Among these preferred regiments, EACS favour

those with a high genetic barrier (DTG or BIC) as a third agent.

Other recommended first-line regimens include one two-drug combination with an NRTI (3TC) plus an INSTI (DTG), and three three-drug combinations with two NRTIs (TAF/FTC, TDF/FTC or TDF/3TC) plus a nonnucleoside reverse transcriptase inhibitor [NNRTI; DOR or rilpivirine (RPV)] or plus a boosted protease inhibitor [PI/b; cobicistat (COBI)- or ritonavir (RTV)-boosted darunavir (DRV/c or DRV/r)] (Table 1).

The alternative regimen recommendations to be used when none of the preferred regimens are available are shown in Table 1.

The following two-drug combinations are recommended as possible switch strategies; 3TC with DTG, DRV/b or boosted atazanavir (ATV/b) or DTG plus RPV.

Table 1 Combination antiretroviral therapy (ART) regimens for treatment-naïve adult people living with HIV (PLWH)

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI (preferred)		
ABC/3TC + DTG	HLA-B*57:01 negative	I (ABC: HLA-B*57:01, cardiovascular risk)
ABC/3TC/DTG	HBsAg negative	
TAF/FTC or TDF/FTC or TDF/3TC + DTG		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) III (Weight increase)
TAF/FTC/BIC		
TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
DTG + 3TC	HBsAg negative HIV VL < 500 000 copies/mL CD4 count > 200 cells/μL	
2 NRTIs + NNRTI		
TAF/FTC or TDF/FTC or TDF/3TC + DOR		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) V (DOR: HIV-2)
TDF/3TC/DOR		
TAF/FTC or TDF/FTC or TDF/3TC + RPV	CD4 count > 200 cells/μL, HIV VL < 100 000 copies/mL	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (RPV: HIV-2)
TAF/FTC/RPV	Not on proton pump inhibitor	
TDF/FTC/RPV	With food	
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/FTC or TDF/3TC + DRV/c or DRV/r	With food	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (DRV/r: cardiovascular risk)
TAF/FTC/DRV/c		
Alternative regimens		
2 NRTIs + INSTI		
ABC/3TC + RAL qd or bid	HBsAg negative HLA-B*57:01 negative	I (ABC: HLA-B*57:01, cardiovascular risk) IV (RAL: dosing)
TDF/FTC/EVG/c	With food	II (TDF: prodrug types. Renal and bone toxicity)
TAF/FTC/EVG/c		VIII (EVG/c: use in renal impairment)
2 NRTIs + NNRTI		
ABC/3TC + EFV	HLA-B*57:01 negative HBsAg negative HIV VL < 100 000 copies/mL At bedtime or 2 h before dinner	I (ABC: HLA-B*57:01, cardiovascular risk) IX (EFV: suicidality. HIV-2 or HIV-1 group 0)
TAF/FTC or TDF/FTC or TDF/3TC + EFV	At bedtime or 2 h before dinner	II TDF: prodrug types. Renal and bone toxicity. TAF dosing) IX (EFV: suicidality. HIV-2 or HIV-1 group 0)
TDF/FTC/EFV		
2 NRTIs + PI/r or PI/c		
ABC/3TC + ATV/c or ATV/r	HLA-B*57:01 negative HBsAg negative HIV VL < 100 000 copies/mL Not on proton pump inhibitor With food	I (ABC: HLA-B*57:01, cardiovascular risk) X (ATV/b and renal toxicity)
ABC/3TC + DRV/c or DRV/r	HLA-B*57:01 negative HBsAg negative With food	I (ABC: HLA-B*57:01, cardiovascular risk) VII (DRV/r and cardiovascular risk)
TAF/FTC or TDF/FTC or TDF/3TC + ATV/c or ATV/r	Not on proton pump inhibitor With food	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) X (ATV/b: renal toxicity)

Table 1 (*Continued*)

Regimen	Main requirements	Additional guidance (footnotes)
Other combinations		
RAL 400 mg bid + DRV/c or DRV/r	HBsAg negative HIV VL < 100 000 copies/mL CD4 > 200 cells/μL With food	VII (DRV/r: cardiovascular risk)

Additional guidance: (I) ABC contraindicated if HLA-B*57:01 positive. Even if HLA-B*57:01 negative, counselling on hypersensitivity reaction risk still mandatory. ABC should be used with caution in persons with a high CVD risk (> 10%). (II) In certain countries, TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate). There are available generic forms of TDF, which instead of fumarate use phosphate, maleate, and succinate salts. They can be used interchangeably. When available, combinations containing TDF can be replaced by the same combinations containing TAF. TAF is used at 10 mg when coadministered with drugs that inhibit p-glycoprotein (P-gp), and at 25 mg when co-administered with drugs that do not inhibit P-gp. The decision whether to use TDF or TAF depends on individual characteristics as well as availability. So far, there are only limited long-term data on TAF. If the antiretroviral (ART) regimen does not include a booster, TAF and TDF have similar short-term risks of renal adverse events leading to discontinuation and bone fractures.
TAF*** should be considered as a first choice**** over TDF in individuals with:
(1) established or high risk of chronic kidney disease (see Guideliness page 64); (2) co-administration of medicines with nephrotoxic drugs or prior TDF toxicity (see Guidelines page 65); (3) osteoporosis/progressive osteopenia, high fracture risk asessement tool score or risk factors (see Guidelines page 61); (4) history of fragility fracture (see Guidelines pages 61 and 63).
***There are limited data on use of TAF with estimated glomerular filtration rate (eGFR) < 30 mL/min;
****Expert opinion pending clinical data.
(III) Two randomized controlled trials (performed in South Africa and Cameroon) showed that, in comparison with EFV, treatment with DTG in naïve persons was associated with increased weight gain when combined with TAF/FTC, TDF/FTC or TDF/3TC. The effect on increased weight was more important for women under treatment containing both DTG and TAF (reference [12], [13] in the Guidelines). (IV) RAL can be given as RAL 400 mg bid or RAL 1200 mg (two 600 mg tablets) qd. Note: RAL qd should not be given in the presence of an inducer (i.e. TB drugs or antiepileptics) or divalent cations (i.e. calcium, magnesium or iron), in which case RAL should be used bid. (V) DOR is not active against HIV-2. (VI) RPV is not active against HIV-2. (VII) A single study has shown an increase in CVD risk with cumulative use of DRV/r (reference [14] in the Guidelines). (VIII) TDF/FTC/EVG/c to be used only if eGFR ≥ 70 mL/min. It is recommended that TDF/FTC/EVG/c is not initiated in persons with eGFR < 90 mL/min unless this is the preferred treatment. (IX) EFV: not to be given if history of suicide attempts or mental illness; not active against HIV-2 and HIV-1 group O strains. (X) Potential renal toxicity with ATV/b.
NRTI, nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; HLA, human leucocyte antigen; ABC, abacavir; HBsAg, hepatitis B virus surface antigen; 3TC, lamivudine; DTG, dolutegravir; TAF, tenofovir alafenamide; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate), BIC, bictegravir; DOR, doravirine; RAL, raltegravir; qd, once daily; bid, twice a day; VL, viral load; RPV, rilpivirine; PI/r, ritonavir-boosted protease inhibitor; PI/c, cobicistat-boosted protease inhibitor; EVG, elvitegravir; NNRTI, nonnucleoside reverse transcriptase inhibitor; ATV, atazanavir; CVD, cardiovascular disease.

Three new tables were included for pregnant women living with HIV or women wishing to conceive to specify which drugs are considered safe and which to avoid. EACS currently recommends not using DTG in women who wish to conceive because of the reported higher risk of neural tube defect if used preconception [3]. As a consequence of insufficient data on safety and efficacy in pregnancy, TAF, RAL once a day (qd), BIC and DOR are currently not recommended in women who become pregnant while on ART. In addition, COBI boosting has proved less robust than RTV boosting during pregnancy, and therefore COBI-boosted elvitegravir (EVG/c) is not recommended and ATV or DRV should be boosted only with RTV in women who become pregnant while on ART. The preferred initial options for ART-naïve pregnant women include combinations of two NRTIs (ABC/3TC, TDF/FTC or TDF/3TC) plus an INSTI [DTG, which can be used after pregnancy week 8, or RAL twice a day (bid)]. The recommended regimens include two NRTIs (TDF/FTC or TDF/3TC) plus a PI/r (DRV/r). Alternative regimens to be considered consist of two NRTIs (ABC/3TC, TDF/FTC or TDF/3TC) plus an NNRTI [efavirenz (EFV) or RPV] or plus a PI/r (ATV/r or DRV/r). A section on labour and breastfeeding was further added.

For PLWH coinfected with susceptible TB, the recommended ART regimens to be used with rifampicin include the combination of two NRTIs (TDF/FTC, TDF/3TC or ABC/3TC) plus an NNRTI (EFV), or for alternative regimens plus an INSTI (DTG bid or RAL bid). An updated table further describes the most relevant DDIs when ART is co-administered with rifampicin or rifabutin.

For post-exposure prophylaxis (PEP), additional regimen combinations with TAF/FTC, RAL qd and BIC were included. For pre-exposure prophylaxis (PrEP), use of daily TAF/FTC was included as a possible alternative in men who have sex with men and transgender women.

Section on DDIs and other prescribing issues

All DDI tables have been organized in a separate section devoted to issues related to prescribing ART and other co-medication in PLWH. The DDI tables each provide an overview of the interaction potential between individual antiretroviral drugs and the most commonly used co-medications within a therapeutic area.

Two new tables have been added on dose adjustment in renal impairment for commonly co-administered drugs

Table 2 Preferred DAA HCV treatment options (except for persons pretreated with protease or NS5A inhibitors)

		Treatment duration and RBV usage		
HCV GT	Treatment regimen	Noncirrhotic	Compensated cirrhotic	Decompensated cirrhotic CTP class B/C
1 and 4	**EBR/GZR**	**12 weeks**[a]		Not recommended
	GLE/PIB	**8 weeks**	**12 weeks**	Not recommended
	SOF/VEL	**12 weeks**		**12 weeks with RBV**
	SOF/LDV ± RBV	**8–12 weeks without RBV**[b]	**12 weeks with RBV**[c]	
2	**GLE/PIB**	**8 weeks**	**12 weeks**	Not recommended
	SOF/VEL	**12 weeks**		**12 weeks with RBV**
3	**GLE/PIB**	**8 weeks**[d]	**12 weeks**[d]	Not recommended
	SOF/VEL ± RBV	**12 weeks**[e]	**12 weeks with RBV**[f] **or 24 weeks without RBV**	
	SOF/VEL/VOX	-	**12 weeks**	Not recommended
5 and 6	**GLE/PIB**	**8 weeks**	**12 weeks**	Not recommended
	SOF/LDV ± RBV	**12 weeks ± RBV**[g]	**12 weeks with RBV**[c]	
	SOF/VEL	**12 weeks**		**12 weeks with RBV**

CTP, child-Turcotte-Pugh; DAA, direct-acting antiviral; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NS5A, Nonstructural protein 5A; OBV, ombitasvir; PIB, pibrentasvir; PTV/r, paritaprevir/RTV; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

[a]Extension of treatment to 16 weeks and addition of RBV in PLWH with GT1a with baseline HCV RNA > 800 000 IU/mL and/or NS5A RASs causing at least 5-fold reduction in activity of EBR to minimize the risk of treatment failure and in HCV GT4-experienced PLWH with HCV RNA > 800 000 IU/mL at 8 weeks can be considered in GT1b treatment-naïve patients with F0–F2.

[b]8 weeks of treatment without RBV only in treatment-naïve PLWH with F < 3 and baseline HCV RNA < 6 million IU/mL.

[c]In persons intolerant to RBV, treatment may be prolonged to 24 weeks. RBV can be omitted in treatment-naïve or -experienced PLWH with compensated cirrhosis without baseline NS5A RAS.

[d]Treatment duration in HCV GT3 who failed previous treatment with interferon (IFN) and RBV ± SOF or SOF and RBV should be 16 weeks.

[e]Addition of RBV in treatment-experienced PLWH with baseline NS5A RASs, if RAS testing available; if these persons are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV.

[f]If RAS testing is available and demonstrates absence of NS5A RAS Y93H, RBV can be omitted in treatment-naïve PLWH with compensated cirrhosis.

[g]In treatment-experienced (exposure to IFN/RBV/SOF) PLWH, treat with RBV for 12 weeks or prolong treatment to 24 weeks without RBV.

in PLWH and a list of the top ten drugs to avoid in elderly PLWH to increase awareness of inappropriate drug administration and dosing.

In addition, a new table was developed on the recommended drug dosages for hormone therapy when used at high doses for gender transitioning.

Detailed information on DDIs can be found in the University of Liverpool website www.hiv-druginteractions.org.

Comorbidity section

The comorbidity section continues to be the largest section of the EACS Guidelines and provides screening and management recommendations for the most common comorbid conditions among PLWH and for conditions that require specific guidance.

Given the increased prevalence of frailty in PLWH, a new table outlines definitions, recommended assessments and management to help identify those at frailty risk. For some comorbidities [e.g. hypertension, nonalcoholic fatty liver disease (NAFLD) and bone disease], different age-specific guidance for diagnosis [e.g. using dual-energy X-ray absorptiometry (DEXA) scan and liver fibrosis scores] and management (e.g. for hypertension) is provided.

Recommendations to lower blood pressure targets to systolic pressure < 130 mmHg and diastolic pressure < 80 mmHg were previously introduced (v9.0) for high-risk individuals; in 2019 (v10.0), these recommendations were further broadened to apply to all PLWH. Furthermore, antihypertensive drug sequencing was amended.

The threshold for ART modification in relation to 10-year predicted cardiovascular disease (CVD) risk has been lowered from 20% to 10%. Similarly, lipid targets have been lowered for both primary and secondary prophylaxis.

As obesity and weight increase have become more frequent in PLWH, and this is a rapidly evolving field, an addition on diagnosis, risk factors and management of obesity was made to the existing chapter on lipoatrophy. New data on weight increase related to use of INSTIs and TAF were added to the table on potential adverse drug effects.

In the liver section, a fourth step was added to the work-up of persons with increased transaminases to include risk stratification using aspartate aminotrabsferase to platelet ratio (APRI), fibrosis-4 (FIB4), NAFLD fibrosis score and transient elastography. Similarly, the screening recommendation for hepatocellular carcinoma in noncirrhotic persons with chronic HBV coinfection was amended in collaboration with the viral hepatitis panel to include an age threshold acknowledging the higher risk in those older than 45 years [4]. The algorithm for surveillance for

varices and primary prophylaxis was updated to incorporate transient elastography (where available) with platelet counts to determine indications for upper gastrointestinal endoscopy. Finally, the diagnostics flow-chart for NAFLD was revised to include the use of fibrosis scores.

Finally, in the renal subsection, it was specified to use urine albumin to creatinine ratio to screen for glomerular disease (such as diabetes and HIV-related disease), and urine protein to creatinine ratio to screen for tubular diseases (i.e. ART drug toxicity). The cut-off values for albuminuria and proteinuria have further been streamlined with the Kidney Disease: Improving Global Outcomes (KDIGO) recommendations [5].

Viral hepatitis coinfection section

This section was renamed *Clinical management and treatment of viral hepatitis co-infections in PLWH*. The overall structure of the section was also revised to improve readability.

The first subsection contains general recommendations on viral hepatitis coinfections in PLWH and focuses on screening recommendations, measures of prevention and complications related to viral hepatitis. A new table on noninvasive liver fibrosis markers was introduced.

Another subsection focuses on treatment and monitoring of PLWH coinfected with HBV and includes a part on HBV reactivation related to immunosuppressive treatment with monitoring and treatment recommendations stratified by type of immunosuppressive drugs. Awareness of the risk for HBV reactivation is particularly important in the era of ART simplification with regimens not containing NRTIs active against HBV.

There were no new direct-acting antivirals (DAAs) licensed for the treatment of HCV since the last Guideline revision. The HCV treatment recommendations table was split into two parts, with one table listing the preferred treatment options, and a second table listing the alternative options (Table 2, 3). The recommendations for the management of DAA treatment failures were updated.

Acute HCV infection was renamed "recently acquired HCV infection" in accordance with the recent European AIDS Treatment Network consensus conference (NEAT) statement [6]. Lack of spontaneous clearance and progression to chronic infection can be predicted reliably by four weeks after diagnosis in those with less than a $2 \times \log_{10}$ reduction in HCV RNA [7]. Accordingly, this situation is considered as early chronic HCV infection and immediate DAA therapy is recommended. DAA treatment is recommended as in treatment-naïve noncirrhotic individuals (except for those with pre-existing liver cirrhosis), as several trials failed to demonstrate noninferiority of shortened treatment courses [6].

Finally, the recommendations on the management of viral hepatitis D and E in PLWH were expanded.

Table 3 DAA HCV treatment options (except for persons pretreated with protease or NS5A inhibitors) to be used if preferred option is not avaible

		Treatment duration and RBV usage		
HCV GT	**Treatment regimen**	**Noncirrhotic**	**Compensated cirrhotic**	**Decompensated cirrhotic CTP class B/C**
1 and 4	OBV/PTV/r + DSV	8[a]–12 weeks in GT 1b	12 weeks in GT 1b	Not recommended
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	24 weeks in GT 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4		Not recommended
	SOF + DCV ± RBV	12 weeks ± RBV[b]	12 weeks with RBV[c]	
	SOF/VEL/VOX	8 weeks[d]	12 weeks	Not recommended
2	SOF + DCV	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks[d]	12 weeks	Not recommended
3	SOF + DCV ± RBV	12 weeks ± RBV[e] or 24 weeks without RBV	24 weeks with RBV	
	SOF/VEL/VOX	8 weeks[d]	12 weeks	Not recommended
5 and 6	SOF + DCV ± RBV	12 weeks ± RBV or 24 weeks without RBV[f]	12 weeks with RBV[c]	
	SOF/VEL/VOX	8 weeks[d]	12 weeks	Not recommended

CTP, child-Turcotte-Pugh; DAA, direct-acting antiviral; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NS5A, Nonstructural protein 5A; OBV, ombitasvir; PIB, pibrentasvir; PTV/r, paritaprevir/RTV; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

[a] 8 weeks of treatment without RBV only in PLWH without cirrhosis.

[b] Addition of RBV in GT1a treatment-experienced PLWH, but not in PLWH without NS5A RASs, if RAS testing is available.

[c] In PLWH intolerant to RBV, treatment may be prolonged to 24 weeks. RBV can be omitted in treatment-naïve or -experienced PLWH with compensated cirrhosis without baseline NS5A RAS.

[d] Extension of treatment to 12 weeks in DAA treatment-experienced PLWH.

[e] Addition of RBV only in treatment-experienced persons with baseline NS5A RASs, if RAS testing available; if these PLWH are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV.

[f] In treatment-experienced (exposure to IFN/RBV/SOF) PLWH, treat with RBV for 12 weeks or prolong treatment to 24 weeks without RBV.

Opportunistic infection (OI) section

A new table is included at the start of the revised OI section, providing guidance on when to start ART in the presence of OIs and in particular TB, cryptococcal meningitis and cytomegalovirus (CMV) end-organ disease.

Also added is a new table on immune reconstitution inflammatory syndrome (IRIS), including definitions of paradoxical and unmasking IRIS, along with recommendations on prevention and management.

For the 2019 update, extensive revisions on how to manage drug-resistant TB in PLWH were made. The recommendations are in line with the most recent World Health Organization (WHO) recommendations to use four, preferably oral and presumed effective TB drugs for the first six months of intensive treatment, followed by treatment with three active drugs for 12–14 months depending on response [8]. In addition, a new table on recommended TB drug doses and key adverse effects has been added.

Also new is the addition of talaromycosis, which is relevant in PLWH who have lived in Asia. The table contains recommendations on diagnosis, treatment and secondary prophylaxis.

Minor edits have been made to the other individual OIs, most importantly for *Pneumocystis jiroveci* pneumonia (PCP) and *Toxoplasma gondii* infection, where primary prophylaxis can now be stopped already at CD4 counts > 100 cells/μL and if viral load has been undetectable for > 3 months. For nontuberculous mycobacteria, primary prophylaxis in the case of a CD4 count < 50 cells/μL is no longer recommended if ART is started.

Conclusions

The 2019 version of the EACS Guidelines has undergone substantial updates in all sections and has been expanded with new sections on DDIs and other prescribing issues in PLWH. The Guidelines are available in four different formats and translated into Chinese, French, German, Japanese, Portuguese, Russian and Spanish.

Appendix 1:

Guidelines Panel Members 2019

Medical secretariat: the EACS Medical Secretariat is responsible for the coordination and update of the EACS guidelines based on the recommendations from the five EACS panels.

Guidelines Chair: Manuel Battegay (Basel, Switzerland); **Guidelines Coordinator:** Lene Ryom (Copenhagen, Denmark).

Panel members:

HIV treatment:

Chair: José Arribas (Madrid, Spain); Vice-Chair: Jean-Michel Molina (Paris, France); *Young Scientist*: Rosa De Miguel Buckley (Madrid, Spain); Antonella d'Arminio Monforte (Milan, Italy), Manuel Battegay (Basel, Switzerland), Margherita Bracchi (London, UK), Nikos Dedes (Athens, Greece), Andrzej Horban (Warsaw, Poland), Christine Katlama (Paris, France), Inga Latysheva (Saint Petersburg, Russia), Jens D. Lundgren (Copenhagen, Denmark), Sheena McCormack (London, UK), Cristina Mussini (Modena, Italy), Anton Pozniak (London, UK), Federico Pulido (Madrid, Spain), François Raffi (Nantes, France), Peter Reiss (Amsterdam, The Netherlands), Hans-Jürgen Stellbrink (Hamburg, Germany), Marta Vasylyev (Lviv, Ukraine).

Drug–drug interactions:

Chair: Catia Marzolini (Basel, Switzerland); *Vice-Chair*: Giovanni Guaraldi (Modena, Italy); Sara Gibbons (Liverpool, UK), Françoise Livio (Lausanne, Switzerland).

Comorbidities:

Chair: Patrick Mallon (Dublin, Ireland); *Vice-Chair*: Alan Winston (London, UK); *Young Scientist*: Aoife Cotter (Dublin, Ireland); Manuel Battegay (Basel, Switzerland), Georg Behrens (Hannover, Germany), Mark Bower (London, UK), Paola Cinque (Milan, Italy), Simon Collins (London, UK), Juliet Compston (Cambridge, UK), Stéphane De Wit (Brussels, Belgium), Leonardo M. Fabbri (Modena, Italy), Christoph A. Fux (Aarau, Switzerland), Magnus Gisslen (Gothenburg, Sweden), Giovanni Guaraldi (Modena, Italy), Justyna D. Kowalska (Warsaw, Poland), Jens D. Lundgren (Copenhagen, Denmark), Esteban Martínez (Barcelona, Spain), Catia Marzolini (Basel, Switzerland), José M. Miro (Barcelona, Spain), Eugenia Negredo (Barcelona, Spain), Neil Poulter (London, UK), Peter Reiss (Amsterdam, The Netherlands), Lene Ryom (Copenhagen, Denmark), Giada Sebastiani (Montreal, Canada).

Viral hepatitis co-infections:

Chair: Andri Rauch (Bern, Switzerland); *Vice-Chair*: Sanjay Bhagani (London, UK); *Young Scientist*: Charles Béguelin (Bern, Switzerland); Juan Berenguer (Madrid, Spain), Christoph Boesecke (Bonn, Germany), Raffaele Bruno (Pavia, Italy), Svilen Konov (London, UK), Karine Lacombe (Paris, France), Stefan Mauss (Düsseldorf, Germany), Luís Mendão (Lisbon, Portugal), Lars Peters (Copenhagen, Denmark), Massimo Puoti (Milan, Italy), Jürgen K. Rockstroh (Bonn, Germany).

Opportunistic infections:

Chair: Ole Kirk (Copenhagen, Denmark); *Vice-Chair*: Paola Cinque (Milan, Italy); *Young Scientist*: Daria

Podlekareva (Copenhagen, Denmark); Juan Ambrosioni (Barcelona, Spain), Nathalie De Castro (Paris, France), Gerd Fätkenheuer (Cologne, Germany), Hansjakob Furrer (Bern, Switzerland), José M. Miro (Barcelona, Spain), Cristiana Oprea (Bucharest, Romania), Anton Pozniak (London, UK), Alain Volny-Anne (Paris, France). WAVE representative: Justyna D. Kowalska (Warsaw, Poland).

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